

**Notice of Allowability**

Application No.

10/804,937

Examiner

Rosanne Kosson

Applicant(s)

ANAND-APTE, BELA

Art Unit

1652

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address--

All claims being allowable, PROSECUTION ON THE MERITS IS (OR REMAINS) CLOSED in this application. If not included herewith (or previously mailed), a Notice of Allowance (PTOL-85) or other appropriate communication will be mailed in due course. **THIS NOTICE OF ALLOWABILITY IS NOT A GRANT OF PATENT RIGHTS.** This application is subject to withdrawal from issue at the initiative of the Office or upon petition by the applicant. See 37 CFR 1.313 and MPEP 1308.

1. ☒ This communication is responsive to an amendment filed on October 6, 2006.
2. ☒ The allowed claim(s) is/are 14-17, 19 and 21.
3. ☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).
- a) ☐ All b) ☐ Some\* c) ☐ None of the:
1. ☐ Certified copies of the priority documents have been received.
2. ☐ Certified copies of the priority documents have been received in Application No. \_\_\_\_\_.
3. ☐ Copies of the certified copies of the priority documents have been received in this national stage application from the International Bureau (PCT Rule 17.2(a)).

\* Certified copies not received: \_\_\_\_\_.

Applicant has THREE MONTHS FROM THE "MAILING DATE" of this communication to file a reply complying with the requirements noted below. Failure to timely comply will result in ABANDONMENT of this application.

**THIS THREE-MONTH PERIOD IS NOT EXTENDABLE.**

4. ☐ A SUBSTITUTE OATH OR DECLARATION must be submitted. Note the attached EXAMINER'S AMENDMENT or NOTICE OF INFORMAL PATENT APPLICATION (PTO-152) which gives reason(s) why the oath or declaration is deficient.
5. ☐ CORRECTED DRAWINGS ( as "replacement sheets") must be submitted.
- (a) ☐ including changes required by the Notice of Draftsperson's Patent Drawing Review ( PTO-948) attached
- 1) ☐ hereto or 2) ☐ to Paper No./Mail Date \_\_\_\_\_.
- (b) ☐ including changes required by the attached Examiner's Amendment / Comment or in the Office action of Paper No./Mail Date \_\_\_\_\_.
- Identifying indicia such as the application number (see 37 CFR 1.84(c)) should be written on the drawings in the front (not the back) of each sheet. Replacement sheet(s) should be labeled as such in the header according to 37 CFR 1.121(d).
6. ☐ DEPOSIT OF and/or INFORMATION about the deposit of BIOLOGICAL MATERIAL must be submitted. Note the attached Examiner's comment regarding REQUIREMENT FOR THE DEPOSIT OF BIOLOGICAL MATERIAL.

**Attachment(s)**

- |  |   |
|--|---|
| 1. <input type="checkbox"/> Notice of References Cited (PTO-892)   | 5. <input type="checkbox"/> Notice of Informal Patent Application                     |
| 2. <input type="checkbox"/> Notice of Draftsperson's Patent Drawing Review (PTO-948)                       | 6. <input type="checkbox"/> Interview Summary (PTO-413),<br>Paper No./Mail Date _____ |
| 3. <input type="checkbox"/> Information Disclosure Statements (PTO/SB/08),<br>Paper No./Mail Date _____    | 7. <input checked="" type="checkbox"/> Examiner's Amendment/Comment                   |
| 4. <input type="checkbox"/> Examiner's Comment Regarding Requirement for Deposit<br>of Biological Material | 8. <input type="checkbox"/> Examiner's Statement of Reasons for Allowance             |
|  | 9. <input type="checkbox"/> Other _____   |

**EXAMINER'S AMENDMENT**

An examiner's amendment to the record appears below. Should the changes and/or additions be unacceptable to applicant, an amendment may be filed as provided by 37 CFR 1.312. To ensure consideration of such an amendment, it MUST be submitted no later than the payment of the issue fee.

1. The application has been amended as follows.

The description of the drawings on pp. 8-9 in the specification is amended as follows.

Fig. 2 shows graphs indicating: (A) Inhibition of VEGF<sub>165</sub> (10 ng/ml)-mediated migration of PAE-KDR cells by recombinant TIMP3 (rTIMP3). (B) Comparison of the effects of rTIMP3, rTIMP1 and BB3103 on VEGF<sub>165</sub>-induced migration of PAE-KDR cells. (C) Migration of PAE-KDR cells expressing TIMP3 (KDR-TIMP3) toward VEGF<sub>121</sub>. (D) Migration of PAE-KDR cells expressing TIMP3 (KDR-TIMP3) toward and VEGF<sub>165</sub>. In all migration experiments, migrating cell number is expressed as mean  $\pm$  s.e.m, of quadruplicate samples. All experiments were done in triplicate. Open symbols, KDR-vector; closed symbols, KDR-TIMP3. \*,  $P < 0.01$ ; \*\*,  $P < 0.05$ .

Fig. 3 shows graphs indicating TIMP3 inhibits VEGF-mediated endothelial cell proliferation. (A) Proliferative response of PAE-KDR cells to VEGF<sub>165</sub> (5 ng/ml; left) and VEGF<sub>121</sub> (30 ng/ml; right). Effects of recombinant TIMP3 (rT3; 0.3  $\mu$ g/ml and 1  $\mu$ g/ml), TIMP1 (rT1; 1  $\mu$ g/ml) and BB3103 (10  $\mu$ M) were examined by pretreatment of cells for 30 min before the addition of VEGF. (B) Effect of TIMP3 (1  $\mu$ g/ml and 5  $\mu$ g/ml) on proliferative response of PAE-PDGFR-13 $\beta$  to PDGF-BB and PAE-FGFR1 to bFGF compared to control. (C) DNA synthesis of endothelial cells in response to VEGF<sub>165</sub>. Effects of rTIMP3, rTIMP2 and synthetic MMP inhibitor were examined by pretreatment of cells before addition of VEGF. [<sup>3</sup>H]thymidine incorporation was measured during the last 5 h of incubation. (D) Analysis of endothelial cell expressing TIMP3. Expression of TIMP3 protein was confirmed by immunoblotting with TIMP3-specific antibody in PAE-KDR cells (top left). Ability of overexpressed TIMP3 to inhibit gelatinases was analyzed by reverse zymography in ECM preparations of PAE-KDR (bottom left) and PAE-PDGFR-13  $\beta$  cells

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(bottom right). (E) Proliferative response of endothelial cells expressing KDR-TIMP3 (left) or PDGFR- $\beta$ -TIMP3 (right) to VEGF<sub>121</sub> and VEGF<sub>165</sub> was compared with response in cells lacking TIMP3 (KDR-vector and PDGFR- $\beta$ -vector, respectively). PDGF-BB (F) Analysis of mouse endothelial cells infected with adenovirus expressing WT-TIMP3 (WT-T3) and TIMP3Cys1-Ser (T3-C1S). Expression of TIMP3 protein was determined by immunoblotting with antibody against TIMP3 (top left). MMP-inhibitory activity was determined by reverse zymography (top right). Corresponding densito-metric quantitation is expressed as arbitrary optical density (OD) units  $\pm$  s.d. ([C]G) DNA synthesis in adenovirus-infected cells in response to VEGF. Effect of expression of 'inactive' TIMP3 on DNA synthesis induced by VEGF was measured by incorporation of [<sup>3</sup>H]thymidine. In all proliferation experiments, total number of cells was counted at 48 h. Proliferating cell number is expressed as means  $\pm$  s.e.m, of quadruplicate samples. DNA synthesis data represent the means  $\pm$  s.e.m, of triplicate samples; similar results were obtained in at least 2 different experiments. \*, P<0.01.

The claims are amended as follows.

1-13. (canceled)

22-31. (canceled)

Authorization for this Examiner's Amendment was given by telephone by Applicant's agent, Mr. Richard Sutkis, on October 25, 2006.

2. The following is an examiner's statement of reasons for allowance. Applicant's amendments to the claims overcome the rejections under 35 USC §112, first and second paragraphs, as well as the rejections under 35 USC §102.

3. Any comments considered necessary by applicant must be submitted no later than the payment of the issue fee and, to avoid processing delays, should preferably accompany the issue fee. Such submissions should be clearly labeled "Comments on Statement of Reasons for Allowance."

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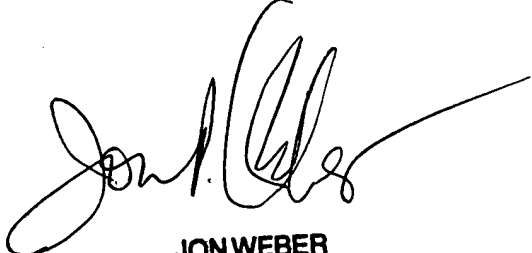
Any inquiry concerning this communication or earlier communications from the examiner should be directed to Rosanne Kosson whose telephone number is 571-272-2923. The examiner can normally be reached on Monday-Friday, 8:30-6:00, alternate Mondays off.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Ponnathapu Achutamurthy can be reached on 571-272-0928. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see <http://pair-direct.uspto.gov>. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

Rosanne Kosson  
Examiner, Art Unit 1652

rk/2006-10-23



**JON WEBER**  
**SUPERVISORY PATENT EXAMINER**